

SCHWARZ//BIOSCIENCES	FORMULATION & TECHNOLOGY REPORT	Date Project No. Incontinence
TITLE TDS for the treatment of incontinence, part III: Delivery of SPM8224, the free base of Fesoterodine CONFIDENTIAL	Page of 1 9	Report No. 30

1. SUMMARY

The report describes in vitro skin permeation characteristics of transdermal delivery systems (TDS) containing SPM8224, the free base of Fesoterodine. Test samples were prepared by either lab-scale solvent coating or hot-melt processing. Patches were tested by means of flux rates across hairless mouse skin, selected samples were also investigated in the LACDR human skin model.

High flux rates of SPM8224 across mouse skin were obtained for all batches. The highest initial flux was achieved with a silicone based hot melt formulation.

Permeation across human skin demonstrated the promising potential of SPM8224, the free base of Fesoterodine, for the treatment of overactive bladder. Based on these in vitro data patches with sizes in the range of 15 to 30 cm² could theoretically deliver 4 to 8 mg/24 h which is the current range of the oral Fesoterodine formulation. The data have to be confirmed in vivo.

Besides this, new acrylic based hot melt adhesive from National Starch & Chemical were evaluated. One very promising formulation could be identified. Provided that other success criteria, such as physico-chemical compatibility with the hot melt process and with different drugs, are met these formulations might fill the gap in hot melt pressure sensitive adhesives for transdermal systems.

Distribution: Original PH DOK F&T, PHA, TS, TL-PH REG, IPM (AS) Summary only/PCD, PH TOX, BA, MOBI, STI, ILF
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Key words:

Fesoterodine, SPM8224, skin permeation in vitro, mouse skin, human skin, hot melt acrylics

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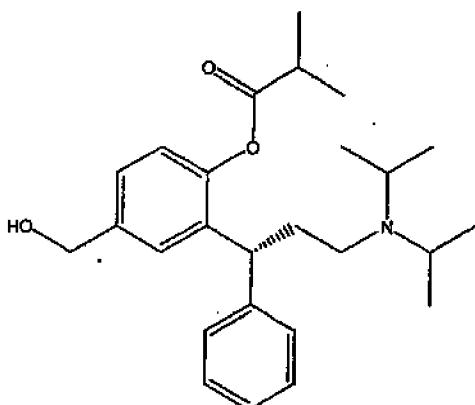
APPENDIX A (Certificates of analysis)

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2. INTRODUCTION AND OBJECTIVES

The objective of the study was to investigate the feasibility of transdermal delivery of SPM8224, the free base of Fesoterodine (scheme 1).



Scheme 1: Chemical structure of the free base of Fesoterodine

Therefore, several lab scale patch batches containing SPM8224 were prepared and investigated by means of in vitro drug permeation across hairless mouse skin. Subsequently, selected samples were investigated in a human skin model, as well.

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3. MATERIALS AND METHODS

For a detailed description of the experiments refer to the batch documentation.

Hot-melt patches (exemplary): 8 g of a preformed silicone adhesive were weighed into a beaker and tempered at 160°C for ca. 20 min to achieve a homogenous melt. 0.5 g of inner phase polymer (e.g. poly(ethylene oxide) and 1.5 g of drug were added. After tempering at 160°C for additional 5 min the mixture was homogenized manually and further processed on the pre-tempered Chill-Roll (120°C, 250 µm) for lamination.

5 cm² patches were isolated by manual punching followed by determination of the average patch weight (n=10). Finally, patches were sealed individually in pouches.

Mouse Skin Model (PHA): according to OBU0469.ABV100, rev. 00 (1998) with an active diffusion area of 2.55 cm², a phosphate buffer acceptor phase at pH 6.2 and a temperature of 32°C, n=3

Human Skin Model (LACDR):

according to H. Tanojo et al., J. Control Rel. 45 (1997) 41-47.

skin from abdomen with a thickness of approx. 250 µm, flux experiment: acceptor phase: PBS, pH= 6.2, temperature: 32°C, diffusion cells with spiral groove (8 cells), groove area: 0.552 cm², dialysis membrane used as separator between skin and acceptor phase flux: 5 ml/hour PBS, experiment runs for 72 hours, sampling cycle: 3 hours

Analytical Methods (PHA): refer to certificates of analysis

Data Analysis: sigmoidal Bolzmann and linear fit: Microcal Origin 6.0

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4. RESULTS AND DISCUSSION

The free base of Fesoterodine is an oily substance and was used with a purity of approx. 90%. Several lab scale patch batches with different compositions were prepared by either solvent coating or hot melt processing and the preparation presented no difficulties. The properties of these batches are summarized in table 1.

Table 1: Properties of the patch batches

No	Lot No. (Ch.B.)	PSA	Theo. drug loading [% (w/w)]	Patch weight (n=10) [g/m ²]
1	20111080	SC acrylic	15	100
2	20111085	HM EVA	15	84
3	20111086	HM silicone	15	63
4	20111087	HM SxS	15	89
5	20111095	HM acrylic 01	15	73
6	20201027	HM acrylic 02	15	121
7	20201028	HM acrylic 03	15	115

SC Acrylic = solvent coating , acrylic type adhesive, Duro Tak 387-2287, National Starch & Chemical (NSC)
 HM EVA = hot melt, ethylene vinyl acetate co-polymer adhesive, Dispofix 213, NSC
 HM Silicone = hot melt silicone based adhesive, BioPSA + 5% (w/w) Ozokerite wax, DowCorning
 HM SxS = hot melt, styrene block co-polymer, in house formulation
 HM Acrylic 0x = hot melt acrylic type adhesives, experimental formulations from NSC, refer to Annex

All batches were tested in the hairless mouse skin model.

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Fig. 1 outlines the cumulative permeation of SPM8224 across hairless mouse skin (HMS) from patches prepared with the most common adhesive classes, acrylic based, ethylene vinyl acetate based (EVA), silicone based and poly(styrene) based (SxS). The flux rates were expressed as permeation of active metabolite, which is the hydrolysis di-hydroxy product (SPM7605).

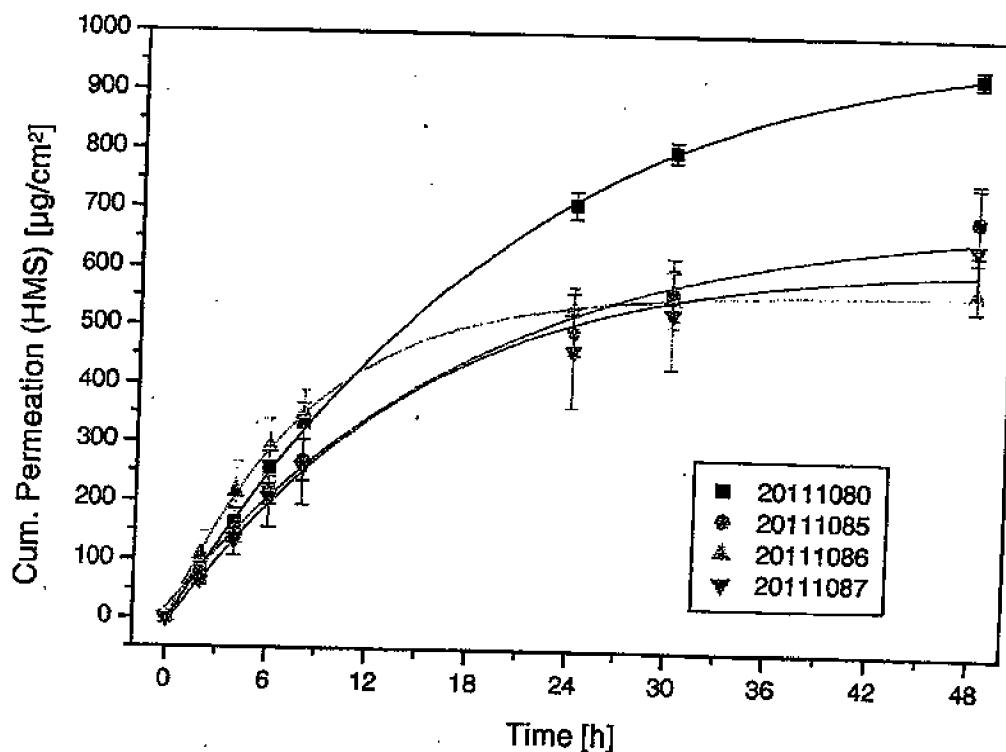


Fig. 1: Cumulative drug permeation (calculated as permeation of active metabolite, SPM7605)

In all cases high flux rates were observed following a non-linear release kinetics. The flux rates from EVA and SxS matrices were nearly identical. Higher initial rates were obtained for the silicone and the acrylic based systems. While the silicone type batch showed the highest drug permeation in the first 6 to 8 h, the subsequent higher values for the acrylic based patch were mainly due to a higher patch weight.

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Fig. 2 illustrates the drug permeation across hairless mouse skin (HMS) from new types of pressure sensitive adhesives (PSA): for the first time it was possible to test the performance of acrylic based patch batches which were prepared by hot melt processing. The three different experimental PSA were exclusively obtained from National Starch & Chemical.

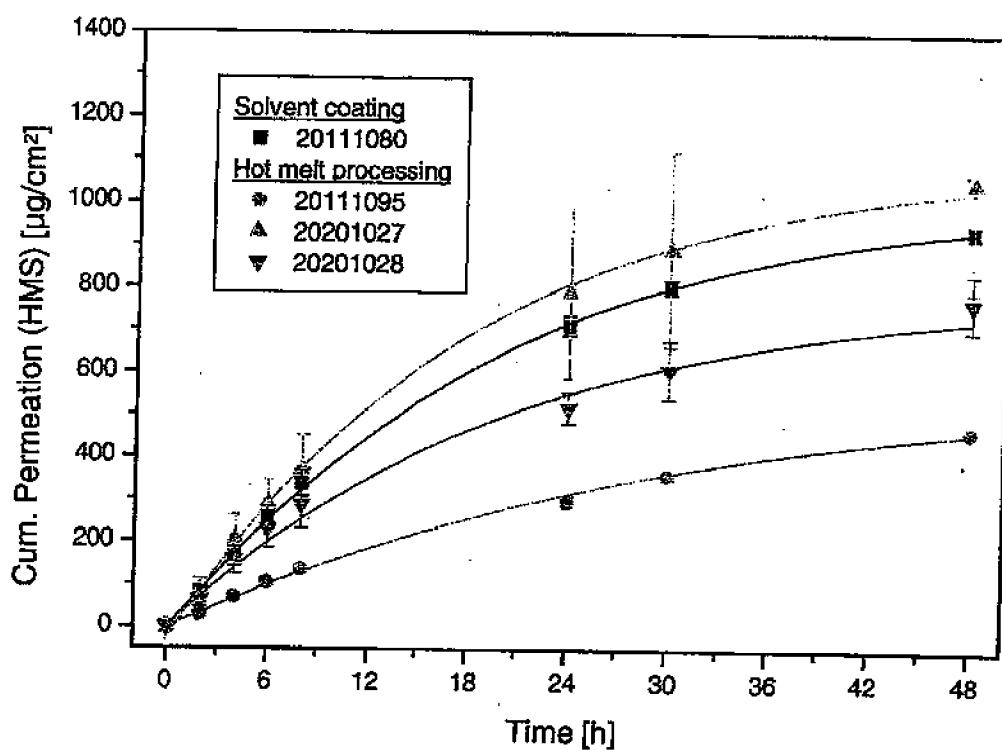


Fig. 2: Cumulative drug permeation (calculated as permeation of active metabolite, SPM7605)

While two of these new PSA (batches 20111095 and 20201028) yielded lower flux rates, it was possible with the third PSA (batch 20201027) to achieve flux rates comparable to the solvent born system (batch 20111080). Although still in an experimental stage this new class of acrylic based PSA seems to be capable of closing the final gap in hot melt processing, since up to now the use of acrylics was limited to solvent coating, only.

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Two batches were investigated in the LACDR human skin model. Since the skin supporting silicone membrane in this model was hindering drug flux it was exchanged with a dialysis membrane. Fig. 3 demonstrates the obtained flux rates across the composite of excised human skin supported with a dialysis membrane (EHS/DM).

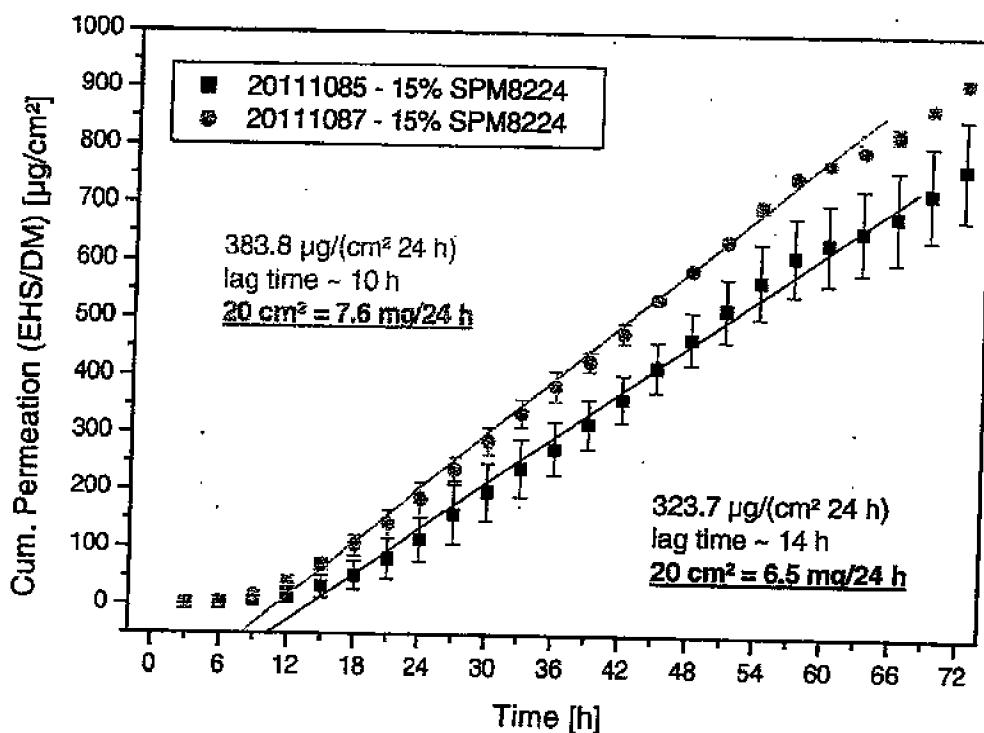


Fig. 3: Cumulative drug permeation (calculated as permeation of active metabolite, SPM7605)

After short lag-times of 6 to 8 h (which are not predictive for the *in vivo* situation) both batches showed a high steady state flux for at least 2.5 d. From these results patches with a size of already 20 cm² could theoretically deliver therapeutic doses of the free base of Fesoterodine, compared to the oral formulation.

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CONCLUSIONS

Several lab scale patch batches containing the free base of Fesoterodine were prepared and tested by means of in vitro drug permeation across mouse skin and human skin.

Based on the results obtained, the flux rates were found to be sufficient for the treatment of overactive bladder with patch sizes in the range of 15 to 30 cm² (equal to ca. 4 to 8 mg/24 h).

Moreover, in cooperation with National Starch & Chemical a new series of hot melt acrylics could be developed. These new adhesives could close an actual gap in hot melt pressure sensitive adhesive (PSA) formulation for transdermal systems. To further evaluate this class of PSA an investigation on physico-chemical compatibility with the hot melt process and different drug substances has to be performed.

ANNEX 1

Copies of the Certificates of Analysis

(signed originals stored at PH DOK)

Analysenzertifikat

in vitro Freisetzung durch Mäusehaut

Präparat : SPM 907 Ch.-B.: 20111080

Wirkstoff : **SPM 8224**

Sollgehalt : 15 %

ABV vom : analog OB 0469.ABV.100

TDS - Fläche: 5 cm²

Analysendatum :

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfäche 2,55 cm²

Mäusehautdicke: 1=161 µm; 2=168µm, 3=172µm, 34,5g

Alter lebend: 8 Wochen, TK-Schrank 10 Wochen SKH-1 ♂

HPLC-Bedingungen:

Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure

Temperatur: 35°

Wellenlänge: 220 nm

Fluss: 1 ml

Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	55,67	84,70	72,02	70,80	14,6
4	122,20	170,16	138,78	143,71	24,4
6	198,00	256,39	218,78	224,39	29,6
8	263,98	330,41	286,25	293,55	33,8
24	501,55	599,45	570,07	557,02	50,2
30	572,00	664,50	646,75	627,75	49,1
48	653,61	738,79	750,20	714,20	52,8

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b) =

74,6 µg

Regressionskoeffizient (m) =

20,83 µg/h

Korrelationskoeffizient (r) =

0,9786 3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	21,74	23,83	19,57	21,71	2,1
4	44,25	48,65	42,13	45,01	3,3
6	69,47	73,58	67,88	70,31	2,9
8	91,83	96,11	88,95	92,30	3,6
24	277,04	239,90	228,10	248,35	25,5
30	312,79	269,83	261,67	281,43	27,5
48	377,09	322,27	327,26	342,21	30,3

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b) =

6,0 µg

Regressionskoeffizient (m) =

10,17 µg/h

Korrelationskoeffizient (r) =

0,9990 3-24h

Datum

Fabert (PHA)

Dr. Seiffert (PHA)

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat : SPM 907 Ch.-B.: 20111085

Wirkstoff : SPM 8224

Sollgehalt : 15 %

ABV vom : analog OB 0469.ABV.100

TDS - Fläche: 5 cm²

Analysendatum :

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfäche 2,55 cm²

Mäusehautdicke: 1=174 µm; 2=159µm, 3=190µm, 35,5g

Alter lebend: 8 Wochen, TK-Schrank 10 Wochen SKH-1 ♂

HPLC-Bedingungen:

Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure

Temperatur: 35°

Wellenlänge: 220 nm

Fluss: 1 ml

Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	58,74	72,97	104,26	78,66	23,3
4	121,08	130,31	162,74	138,04	21,9
6	188,37	183,76	239,35	203,82	30,8
8	238,21	223,26	286,98	249,48	33,3
24	410,84	379,08	463,27	417,73	42,5
30	470,84	428,55	518,49	472,63	45,0
48	572,15	507,03	629,89	569,69	61,5

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b) =

92,7

µg

Regressionskoeffizient (m) =

14,19

µg/h

Korrelationskoeffizient (r) =

0,9641

3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	14,65	18,20	20,52	17,79	3,0
4	32,93	34,65	34,64	34,07	1,0
6	52,29	50,29	53,65	52,07	1,7
8	67,36	52,25	66,03	61,88	8,4
24	163,98	136,16	146,39	148,84	14,1
30	187,17	156,71	164,01	169,30	15,9
48	246,26	207,59	207,87	220,57	22,2

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b) =

12,1

µg

Regressionskoeffizient (m) =

5,77

µg/h

Korrelationskoeffizient (r) =

0,9961

3-24h

Datum

Fabert (PHA)

Dr. Seiffert (PHA)

Analysenzertifikat

in vitro Freisetzung durch Mäusehaut

Präparat : SPM 907 TDS Ch.-B.: 20111086
 Wirkstoff : SPM 8224
 Sol Gehalt : 15% TDS - Fläche: 5 cm²
 ABV vom : analog OB 0469.ABV.100 Analysendatum :

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfäche 2,55 cm²
 Mäusehautdicke: 1=188 µm; 2=172µm, 3=167µm, 32,7g
 Alter lebend: 9 Wochen, TK-Schrank 7 Wochen SKH-1 ♂
HPLC-Bedingungen:
 Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
 Temperatur: 35°
 Wellenlänge: 220 nm
 Fluss: 1 ml
 Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	151,6	86,7	72,8	103,7	42,0
4	264,1	194,6	165,7	208,1	50,6
6	329,6	274,1	234,0	279,2	48,0
8	370,9	340,3	291,7	334,3	39,9
24	438,3	538,7	479,3	485,5	50,5
30	442,8	556,4	503,5	500,9	56,8
48	444,3	563,8	521,3	509,8	60,6

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b) = 150,3 µg
 Regressionskoeffizient (m) = 14,98 µg/h
 Korrelationskoeffizient (r) = 0,9227 3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	28,0	18,2	18,3	21,5	5,6
4	52,4	37,3	38,3	42,7	8,5
6	69,4	51,7	53,3	58,1	9,8
8	82,4	64,3	66,5	71,1	9,8
24	127,3	122,2	138,2	129,2	8,1
30	131,6	130,6	149,8	137,3	10,8
48	135,5	138,8	162,2	145,5	14,6

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b) = 24,8 µg
 Regressionskoeffizient (m) = 4,51 µg/h
 Korrelationskoeffizient (r) = 0,9763 3-24h

Analysenzertifikat

in vitro Freisetzung durch Mäusehaut

Präparat : SPM 907 Ch.-B.: 20111087

Wirkstoff : **SPM 8224**

Sollgehalt : 15 %

ABV vom : analog OB 0469.ABV.100

TDS - Fläche: 5 cm²

Analysendatum : 2011-10-27

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfäche 2,55 cm²

Mäusehautdicke: 1=170 µm; 2=162µm, 3=160µm, 31,3g

Alter lebend: 8 Wochen, TK-Schrank 10 Wochen SKH-1 ♂

HPLC-Bedingungen:

Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure

Temperatur: 35°

Wellenlänge: 220 nm

Fluss: 1 ml

Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1·cm²

Zeit [h]	1	2	3	MW	SD
2	44,72	59,11	64,84	56,22	10,4
4	85,65	140,79	132,93	119,79	29,8
6	121,63	218,35	205,37	181,78	52,5
8	150,10	269,83	254,75	224,89	65,2
24	257,35	417,04	435,07	369,82	97,8
30	317,34	466,51	490,29	424,71	93,7
48	384,12	541,07	603,89	509,69	113,2

MW = Mittelwert

SD = Standardabweichung

Achsenabschnitt (b)= 77,2 µg

Regressionskoeffizient (m)= 12,87 µg/h

Korrelationskoeffizient (r)= 0,9521 3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	17,57	20,90	16,42	18,30	2,3
4	33,57	45,48	32,25	37,10	7,3
6	49,28	70,25	50,44	56,66	11,8
8	62,80	89,55	64,09	72,15	15,1
24	137,51	190,84	138,64	155,66	30,5
30	157,04	214,82	156,88	176,25	33,4
48	204,06	268,98	203,75	225,60	37,6

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)= 15,3 µg

Regressionskoeffizient (m)= 5,98 µg/h

Korrelationskoeffizient (r)= 0,9908 3-24h

Datum

Fabert (PHA)

Dr.Seiffert (PHA)

Analysenzertifikat

in vitro Freisetzung durch Mäusehaut

Präparat : SPM 907 TDS

Ch.-B.: 20111095

Wirkstoff : SPM 8224

Sollgehalt : 15%

TDS - Fläche: 5 cm²

ABV vom : analog OB 0469.ABV.100

Analysendatum :

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfläche 2,55 cm²
 Mäusehautdicke: 1=182 µm; 2=169 µm, 3=176 µm, 32,9 g
 Alter lebend: 9 Wochen, TK-Schrank 7 Wochen SKH-1 ♂

HPLC-Bedingungen:

Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure

Temperatur: 35°

Wellenlänge: 220 nm

Fluss: 1 ml

Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	25,7	18,1	21,6	21,8	3,8
4	59,7	47,3	51,8	52,9	6,3
6	87,4	69,2	77,4	78,0	9,1
8	110,2	94,2	100,3	101,6	8,1
24	199,6	212,8	211,4	207,9	7,3
30	253,2	245,3	245,5	248,0	4,5
48	322,0	313,3	318,8	318,1	4,4

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)= 22,4 µg

Regressionskoeffizient (m)= 7,96 µg/h

Korrelationskoeffizient (r)= 0,9849 3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	11,9	10,9	10,7	11,2	0,6
4	26,9	26,7	24,3	26,0	1,4
6	40,0	38,9	35,6	38,2	2,3
8	51,3	52,1	45,7	49,7	3,5
24	112,7	131,2	121,5	121,8	9,3
30	151,7	155,3	140,9	149,3	7,5
48	198,4	210,1	189,2	199,2	10,5

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)= 6,5 µg

Regressionskoeffizient (m)= 4,87 µg/h

Korrelationskoeffizient (r)= 0,9965 3-24h

Datum

Sachbearbeiter(in)(PHA)

Projektgruppenleiter (PHA)

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat : SPM 907 TDS Ch.-B.: 20201027
 Wirkstoff : SPM 8224
 Sollgehalt : 15% TDS - Fläche: 5 cm²
 ABV vom : analog OB 0469.ABV.100 Analysendatum :
Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfäche 2,55 cm²
 Mäusehautdicke: 1=150 µm; 2=148 µm, 3=158 µm, 29,4g
 Alter lebend: 8 Wochen, TK-Schrank 12 Wochen SKH-1 ♂
HPLC-Bedingungen:
 Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
 Temperatur: 35°
 Wellenlänge: 220 nm
 Fluss: 1 ml
 Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	51,3	109,4	80,4	80,4	29,0
4	129,0	217,5	232,3	192,9	55,9
6	208,8	300,8	308,0	272,5	55,3
8	261,7	364,5	422,5	349,6	81,5
24	549,2	591,4	966,0	702,2	229,4
30	634,2	633,6	1081,0	782,9	258,1
48	801,5	680,0	1236,8	906,1	292,8

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)= 87,0 µg
 Regressionskoeffizient (m)= 26,42 µg/h
 Korrelationskoeffizient (r)= 0,9836 3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	14,1	20,5	17,3	17,3	3,2
4	32,2	41,9	56,9	43,7	12,5
6	49,3	59,5	73,1	60,6	12,0
8	65,2	77,4	93,1	78,6	14,0
24	180,8	217,9	213,9	204,2	20,3
30	216,1	248,6	256,0	240,2	21,2
48	284,6	290,7	313,5	296,3	15,2

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)= 8,4 µg
 Regressionskoeffizient (m)= 8,24 µg/h
 Korrelationskoeffizient (r)= 0,9978 3-24h

Datum

Fabert (PHA)

Dr.Seiffert (PHA)

Analysenzertifikat

in vitro Freisetzung durch Mäusehaut

Präparat: SPM 907 Ch.-B.: 20201028
 Wirkstoff: SPM 8224
 Sollgehalt: 15% TDS - Fläche: 5 cm²
 ABV vom: analog OB 0469.ABV.100 Analysendatum:
Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfäche 2,55 cm²
 Mäusehautdicke: 1=158 µm; 2=168µm, 3=171µm, 31,4g
 Alter lebend: 8 Wochen, TK-Schrank 12 Wochen SKH-1 ♂
HPLC-Bedingungen:
 Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
 Temperatur: 35°
 Wellenlänge: 220 nm
 Fluss: 1 ml
 Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	67,0	46,4	9,0	40,8	29,4
4	166,9	120,0	23,2	103,4	73,3
6	240,8	177,4	33,6	150,6	106,2
8	294,4	217,3	39,8	183,8	130,6
24	314,8	282,5	41,1	212,8	149,6
30	370,7	318,0	43,0	243,9	176,0
48	445,8	418,3	48,1	304,1	222,1

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)= 84,4 µg
 Regressionskoeffizient (m)= 6,13 µg/h
 Korrelationskoeffizient (r)= 0,7917 3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	18,4	13,9	6,7	13,0	5,9
4	40,8	33,6	15,1	29,9	13,3
6	60,8	51,1	21,3	44,4	20,6
8	80,3	67,0	26,9	58,1	27,8
24	282,3	256,8	86,4	208,5	106,5
30	347,9	294,7	93,9	245,5	134,0
48	444,3	372,3	117,1	311,2	171,9

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)= -8,1 µg
 Regressionskoeffizient (m)= 8,96 µg/h
 Korrelationskoeffizient (r)= 0,9990 3-24h

Diffusion experiment with SPM 907 patches on full human skin

Experiment number: 907DF004

Purpose of the study:

To investigate the permeation rate of SPM 907 through skin from two newly formulated patches.

Patch:

Active Ingredient: SPM 907

Batch numbers: 20111085 and 20111087

Patch area: 5 cm²

Active ingredient content: 15% SPM 8224

Skin donor:

Birth date: 1964

Sex: female

Skin from: abdomen (belly)

Thickness of dermatomised skin: approximately 250 µm

Diffusion experiment:

Date:

Used cells:

diffusion cells with spiral groove (n=8); groove area: 0.552 cm²

Separator between acceptor phase and skin/patch:

Diachema dialysis membrane, type 10.14, supplied by Dianorm, München, Germany.

Manufactured from neutral cellulose, molar weight cut-off: 5000; thickness (dry): 25 µm.

Pretreated according to the manufacturer's recommendations.

Diameter of separator, skin and patch punch-outs: 1.8 cm.

Setup diffusion cells:

Cell nr.	Cells with/without skin	Batch
1 & 2	with	20111085
3 & 4	with	20111087
5 & 6	without	20111085
7 & 8	without	20111087

Acceptor phase: PBS pH=8.2

Measured temperature waterbath: 32,0 °C

Flux of acceptor phase: 5 ml/hour

Total duration of the experiment: 72 hours, samples are collected in 3 hour periods.

Observations during dermatomisation, cell assembly, disassembly, etc.

Some of the glue from the patch disks destined for cells 7 and 8 remained on the protective foil.

Mass and volume data on the collected fractions

measured density of the used acceptor phase:		1,007 g/ml

Faktor zur Umrechnung auf cm²=

1,812

Flux time (hours)	cell nr.	mass tubes (g) empty	volume fractions (ml)	8224		Fraction = 1.812	DIOH volume	FractionxF kg/cm ²	Mittelwert
				kg/m	kg/n				
3	1	16.946	33.389	16.329	0,00	0,000	0,000	0,327	0,582
	2	17.037	32.858	15.810	0,00	0,000	0,000	0,158	0,286
	3	17.103	32.928	15.715	0,00	0,000	0,000	0,314	0,439
	4	17.146	32.859	15.703	0,00	0,000	0,000	0,314	0,569
	5	17.010	33.141	16.019	11,90	190,625	345,412	0,84	13,456
	6	17.147	32.685	15.410	14,83	230,073	416,893	381,152	24,382
6	7	17.058	32.382	15.217	19,95	305,589	550,103	1,51	17,105
	8	17.132	32.816	15,575	22,77	354,842	642,612	596,357	22,978
	1	16.652	39.032	16,266	0,01	0,163	0,295	0,10	27,723
	2	16.782	32.711	16,818	0,00	0,000	0,000	1,827	50,235
	3	16.689	32.554	15,755	0,01	0,158	0,285	0,09	41,637
	4	17.020	32.867	15,737	0,01	0,157	0,285	0,19	45,936
9	5	17.187	33.320	16.021	8,16	130,730	236,983	0,60	9,613
	6	17.126	32.667	16.433	5,93	91,518	185,830	201,356	17,418
	7	16.897	32.273	15.269	6,88	105,052	190,353	0,67	10,340
	8	17.104	32.806	15,583	8,18	127,550	231,120	210,737	5,416
	1	17.069	33.458	16.275	0,02	0,326	0,590	0,22	3,994
	2	17.072	32.971	15,788	0,00	0,000	0,000	0,285	18,077
12	3	17.137	33.008	15,761	0,03	0,473	0,867	0,54	2,959
	4	17.065	32.888	15,713	0,04	0,629	1,139	0,998	8,245
	5	17.162	33.284	16.020	5,80	92,916	168,362	0,63	14,941
	6	17.095	32.663	15,460	5,89	91,058	164,997	166,680	9,886
	7	17.043	32.447	15,297	6,32	98,677	175,178	0,48	16,370
	8	17.083	32.789	15,597	6,04	94,205	170,699	172,939	10,974
12	1	16.841	33.300	16,245	0,05	0,812	1,472	0,49	12,886
	2	16.877	32.756	15,769	0,01	0,158	0,286	0,879	12,974
	3	17,152	32.980	15,718	0,05	0,788	1,424	0,44	13,006
	4	17.089	32.896	15,697	0,08	1,256	2,275	1,850	17,501
	5	17.086	33.224	16.026	7,93	112,662	204,143	0,79	22,470
	6	16.987	32.537	15,442	4,95	76,437	138,505	171,324	9,615
	7	16.878	32.247	15,282	8,07	123,166	223,176	0,38	17,423
	8	17.293	32.989	15,597	4,81	75,021	135,938	179,557	10,633

1	17,050	33,415	16,251	0,08	1,300	2,356	0,58	9,426	17,079
2	17,230	33,132	15,791	0,04	0,632	1,145	1,750	0,34	5,369
3	17,235	33,082	15,737	0,17	2,675	4,848	1,20	18,884	34,218
4	17,340	33,167	15,717	0,13	2,043	3,702	4,275	1,04	16,346
5	17,254	33,376	16,010	0,56	56,995	103,276	0,30	4,803	29,518
6	16,879	32,401	15,414	4,70	72,446	131,273	117,274	0,36	5,549
7	17,091	32,476	15,278	5,02	76,696	138,973	0,43	6,570	10,055
8	17,301	33,003	15,593	4,15	64,710	117,235	128,114	0,35	11,904
1	16,756	33,089	16,219	0,12	1,946	3,527	0,69	11,191	10,897
2	16,706	32,561	15,745	0,08	1,260	2,282	2,905	0,51	8,030
3	17,087	32,910	15,733	0,16	2,517	4,561	0,84	13,216	14,550
4	16,644	32,417	15,663	0,19	2,976	5,393	4,977	1,20	23,947
5	17,139	33,226	15,975	3,94	62,942	114,051	0,31	4,952	20,273
6	16,988	32,533	15,437	4,28	66,070	119,719	116,885	0,36	5,557
7	16,756	32,129	15,266	4,02	61,370	111,202	0,35	5,343	10,070
8	17,198	32,872	15,566	9,65	56,812	102,944	107,073	0,34	9,682
1	17,056	33,287	16,118	0,21	3,385	6,133	1,08	17,408	29,003
2	17,178	32,924	15,637	0,13	2,033	3,683	4,908	0,69	10,789
3	17,124	32,859	15,626	0,22	3,438	6,229	1,02	15,938	17,414
4	16,860	32,564	15,595	0,25	3,899	7,064	6,647	1,31	28,880
5	17,110	33,120	15,899	3,60	57,235	103,710	0,35	5,565	9,522
6	17,040	32,454	15,307	3,57	54,645	99,018	101,364	0,35	5,357
7	17,224	32,489	15,159	3,12	47,296	85,700	0,33	5,002	9,708
8	17,244	32,821	15,469	3,32	51,356	93,057	89,379	0,34	9,895
1	17,187	33,397	16,097	0,24	3,863	7,000	1,03	16,580	9,636
2	17,224	32,953	15,620	0,20	3,124	5,661	6,330	0,92	14,370
3	17,135	32,842	15,598	0,29	4,523	8,196	1,17	18,249	25,546
4	17,061	32,729	15,659	0,31	4,823	8,740	8,468	1,40	21,763
5	17,198	33,183	15,874	2,90	46,034	83,414	87,333	0,28	4,446
6	17,100	32,514	15,307	3,29	50,360	91,251	0,33	5,051	10,983
7	16,988	32,244	15,150	2,83	42,874	77,688	0,31	4,696	9,708
8	17,085	32,657	15,484	2,81	43,453	78,737	78,213	0,29	4,484
1	16,964	33,063	16,086	0,40	6,435	11,659	1,54	24,773	36,269
2	17,205	32,938	15,624	0,25	3,906	7,078	9,368	1,03	8,054
3	16,647	32,340	15,584	0,45	7,013	12,707	1,67	16,092	28,041
4	17,273	32,939	15,567	0,94	5,289	9,584	11,146	1,40	9,153
5	17,220	33,197	15,866	3,29	51,247	92,860	0,32	5,077	8,603
6	17,038	32,460	15,315	2,54	38,900	70,486	81,673	0,25	3,829
7	17,177	32,434	15,151	3,13	47,422	85,928	0,35	5,303	9,609
8	17,055	32,618	15,455	2,31	35,701	84,690	75,310	0,23	3,555

1	17,231	33,423	16,079	0,58	9,326	16,899	1,46	23,476	42,538	
2	17,188	32,892	15,595	0,54	8,421	15,259	1,48	23,080	41,822	
3	17,012	32,710	15,589	0,78	12,159	22,033	1,79	27,904	50,562	
4	16,846	32,508	15,553	0,50	7,777	14,091	1,37	21,308	38,610	
45	5	17,229	33,189	15,848	1,64	25,992	47,098	0,15	2,377	4,308
6	17,043	32,472	15,322	2,86	43,820	79,402	69,250	0,26	3,984	7,218
7	16,917	32,174	15,151	1,86	28,181	51,064	0,19	2,879	5,216	
8	16,937	32,504	15,459	1,88	29,063	52,661	51,862	0,19	2,937	5,322
48	1	17,121	33,287	16,054	0,56	8,980	16,290	1,33	21,351	38,689
2	17,033	32,737	15,595	0,49	7,641	13,846	15,068	1,28	19,961	36,170
3	13,258	28,961	15,584	0,53	9,818	17,790	1,32	20,571	37,428	
4	17,334	32,980	15,537	0,53	8,235	14,921	16,356	1,35	20,975	38,007
5	16,892	32,943	15,840	1,89	29,938	54,247	0,18	2,851	5,166	
6	17,235	32,627	15,285	2,19	33,474	60,655	57,451	0,19	2,904	5,262
7	17,271	32,491	15,114	1,99	30,077	54,500	0,21	3,174	5,751	
8	17,118	32,677	15,451	1,88	29,048	52,634	53,587	0,19	2,936	5,319
51	1	16,971	32,878	15,796	0,62	9,794	17,748	1,49	23,537	42,648
2	17,206	32,633	15,320	0,46	7,047	12,769	15,258	1,22	18,690	33,866
3	16,917	32,348	15,324	0,65	9,960	18,048	1,36	20,840	37,753	
4	16,955	32,359	15,297	0,49	7,495	13,582	15,815	1,30	19,886	36,038
5	16,957	32,339	15,573	1,68	25,851	46,842	0,26	4,049	7,337	
6	16,943	32,091	15,043	1,99	29,935	54,242	50,542	0,30	4,513	8,177
7	16,703	31,683	14,876	1,74	25,884	46,902	0,29	4,314	7,817	
8	16,994	32,289	15,189	1,60	24,302	44,035	45,468	0,25	3,797	6,880
1	17,029	32,929	15,789	0,65	10,263	18,597	1,48	23,368	42,344	
2	16,939	32,369	15,323	0,47	7,202	13,049	15,823	1,19	18,234	33,040
3	17,242	32,676	15,327	0,71	10,882	19,718	1,38	21,151	38,325	
4	14,706	30,071	15,268	0,74	11,291	20,459	20,089	1,87	28,533	51,701
5	16,986	32,659	15,564	1,95	30,350	54,994	0,00	0,000	0,000	45,013
6	17,068	32,291	15,060	1,92	28,914	52,393	53,693	0,28	4,217	7,641
7	17,187	32,196	14,905	1,55	23,102	41,861	0,26	3,875	7,022	
8	17,233	32,553	15,214	1,58	24,037	43,556	42,708	0,25	3,803	6,892
54	1	16,802	32,815	15,802	0,51	8,059	14,603	1,16	18,331	33,215
2	17,234	32,686	15,345	0,44	6,752	12,234	13,419	1,11	17,032	30,863
3	17,151	32,599	15,341	0,71	10,892	19,736	1,37	21,017	38,082	
4	16,850	32,251	15,294	0,49	7,494	13,579	16,658	1,24	18,964	34,364
57	5	16,890	32,590	15,581	1,99	31,026	56,219	0,37	5,769	10,453
6	16,504	31,674	15,085	1,22	18,379	33,302	44,761	0,21	3,164	5,732
7	17,102	32,116	14,910	0,99	14,761	26,746	0,19	2,833	5,133	
8	16,743	32,020	15,171	0,70	10,620	19,243	22,994	0,13	1,972	3,574

	1	16,951	32,870	15,808	0,27	4,268	7,734	0,58	9,169	16,614
	2	17,105	32,547	15,335	0,23	3,527	6,381	7,062	0,54	8,281
	3	17,156	32,622	15,359	0,32	4,915	8,906	0,57	8,755	15,005
	4	17,103	32,519	15,309	0,25	3,827	6,935	7,920	0,61	9,338
	5	17,084	32,787	15,694	0,68	10,604	19,214	0,12	1,871	15,864
	6	17,049	32,196	15,042	0,83	12,485	22,622	20,918	0,14	2,106
	7	16,993	32,005	14,908	0,68	10,137	18,369	0,13	1,938	16,921
	8	17,108	32,416	15,201	0,67	10,184	18,454	18,411	0,13	1,976
	1	17,163	33,081	15,807	0,28	4,426	8,020	0,57	9,010	3,391
	2	17,025	32,478	15,346	0,23	3,529	6,385	7,208	0,53	8,133
	3	17,136	32,563	15,320	0,32	4,902	8,883	7,007	0,56	8,579
	4	17,104	32,511	15,300	0,25	3,825	6,931	7,907	0,58	8,874
	5	16,849	32,534	15,576	0,66	10,280	18,628	0,12	1,869	16,080
	6	16,974	32,129	15,050	0,81	12,190	22,089	20,358	0,14	2,107
	7	16,955	1,572	14,905	0,66	9,838	17,826	0,13	1,938	14,737
	8	17,163	32,473	15,204	0,65	9,882	17,907	17,866	0,12	1,824
	1	17,088	32,994	15,795	0,39	6,160	11,162	0,77	12,162	22,038
	2	16,922	32,375	15,346	0,25	3,836	6,952	9,057	0,55	8,440
	3	17,115	32,562	15,340	0,33	5,062	9,172	0,63	8,130	3,602
	4	16,603	32,021	15,311	0,39	5,971	10,820	9,896	1,03	15,770
	5	17,196	32,888	15,583	1,29	20,102	36,425	0,23	3,564	3,408
	6	17,124	32,253	15,024	1,57	23,587	42,740	39,683	0,27	6,494
	7	16,883	31,869	14,882	1,23	18,305	33,168	0,24	4,056	15,293
	8	17,174	32,488	15,209	1,23	18,707	33,896	33,532	0,23	3,498
	1	16,919	32,835	15,805	0,55	8,693	15,752	1,04	16,438	21,654
	2	17,089	32,527	15,331	0,47	7,205	13,056	14,404	1,01	15,484
	3	17,259	32,729	15,362	0,73	11,215	20,321	1,16	17,820	18,666
	4	16,857	32,264	15,300	0,50	7,650	13,862	17,091	1,11	16,983
	5	17,196	32,863	15,558	1,26	19,603	35,521	0,23	3,578	30,773
	6	17,075	32,272	15,991	1,48	22,335	40,471	37,996	0,26	3,924
	7	17,161	32,188	14,923	1,35	20,145	36,504	0,26	3,880	28,921
	8	17,244	32,554	15,204	1,18	17,940	32,508	34,506	0,22	3,345
	1	16,950	32,857	15,796	0,60	9,478	17,174	1,10	17,376	31,532
	2	16,787	32,230	15,336	0,47	7,208	13,060	15,117	0,99	15,182
	3	17,186	32,629	15,336	0,86	10,122	18,340	0,26	3,880	6,546
	4	17,196	32,621	15,318	0,48	7,353	13,323	15,831	1,06	16,237
	5	17,192	32,892	15,591	1,18	18,397	33,336	0,21	3,274	28,605
	6	17,092	32,273	15,075	1,39	20,955	37,970	35,653	0,24	3,618
	7	17,168	32,186	14,914	1,18	17,598	31,888	0,22	3,281	6,556
	8	16,958	32,256	15,192	1,14	17,318	31,381	31,634	0,21	3,190
										5,863